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Remarks

Amendments to the Specification

Page 1, line 23, has been amended to insert a "", before granulocyte stimulating factor.

Page 6, line 4, the abbreviation of TNFR has been corrected.

Rejection under 35 U.S.C. 103

Claims 1-3, 6, 8-11, and 17-22 were rejected under 35 U.S.C. 103(a) as obvious over Selinsky, et al., Immunology 94(1):88-93 (1998) in combination with Van Zee, et al., Proc. Natl. Acad. Sci. USA (1992) in view of U.S. Patent No. 4,708,713 to Lentz and U.S. Patent No. 6,017,527. Claim 5 was rejected under 35 U.S.C. 103 over Selinsky, Van Zee, Lentz, Maraskovsky and Feinman, et al., J. Immunol. 138:635 (1987). Claim 10 was rejected under 35 U.S.C. 103 as obvious over Selinsky, Van Zee, Lentz, Maraskovsky, and Goodman. These rejections are respectfully traversed.

Lentz

Lentz describes removal of a large number of proteins using a filter. The only selectivity is by virtue of the molecular weight cutoff of the filter, which is approximately 200,000. ALL proteins in the plasma with the possible exception of some IgM will pass through a filter with a cutoff of 200,000. Therefore the limitations of claims 1-5, 8, 12 and 20 are not met.

Assuming the examiner meant to make a rejection under 35 U.S.C. 103, Selinsky does not make up for the deficiency of Lentz. Lentz teaches away from the selective removal of soluble cytokine receptor molecules. **Lentz states that the immune inhibitor which is being removed is believed to be a high molecular weight**

compound, not a soluble cytokine inhibitor such as soluble TNF receptor, which has a significantly lower molecular weight. Moreover, Lentz clearly does not know what the inhibitor(s) are, indicating that there are more than one inhibitor. In summary, Lentz teaches one of ordinary skill in the art that (1) the inhibitors are high molecular weight proteins and (2) there are more than one inhibitors involved in immunosuppression of the anti-tumor response.

Selinsky

Selinksky describes an experiment to correlate the levels of soluble tissue necrosis factor receptor ("sTNFR") with tumor burden. This in no way makes obvious the removal of sTNFR to treat tumors or other disorders. The standard under 35 U.S.C. 103 is whether the prior art leads one of ordinary skill in the art to combine the prior art as applicant has done, ***with a reasonable expectation of success.***

The prior art at the time this application was filed in May 1998, was that there were a number of tumor markers that correlated with tumor burden. The most well known include the prostate specific antigen ("PSA") and carcinoembryonic antigen ("CEA"). Studies had been conducted to remove both PSA and CEA, with the hope of decreasing tumor burden. Neither had been effective. Therefore, one skilled in the art would have had noexpectation of success that removal of a soluble cytokine receptor such as sTNFR would be effective.

Indeed, this is clearly the opinion shared by the authors of the paper. Enclosed is a copy of the Declaration under 37 C.F.R. 1.132 filed in U.S.S.N. 09/444,144, which subsequently issued as U.S. Patent No. 6,379,708 to Howell, et al. The examiner's

attention is drawn to pages 2-3 of the declaration, discussing first the Lentz patent and then the Selinksky paper. As the authors of the Selinsky paper noted:

"It is submitted that, although the statement in Selinsky et al. may cause one of skill in the art to consider how to antagonize or remove sTNFR1 *in situ*, such a statement is merely an invitation to experimentation and opens the door for one of skill in the art to consider a wide range of possible approaches. Indeed, Selinsky et al. provides absolutely no guidance as to how one of skill in the art would go about such a task, but rather generally state that the "therapeutic utility of manipulating sTNFRI levels *in vitro* has been demonstrated" and that "sTNFRI effectively inhibits immune responses *in vivo* and ...its modulation is a legitimate therapeutica avenue." It is submitted that one of skill in the art, when presented with an invitation to manipulate the effects of a soluble protein, would look to a variety of conventional approaches to remove or manipulate the effects of that soluble protein *in vivo*, because such approaches are the most clinically desirable means of treating a patient."

Van Zee

Van Zee merely reports that soluble receptors for TNF are present during inflammation and that excessive TNF present during the inflammation can be neutralized by binding to soluble TNF receptors.

This reference therefore ***teaches away from what is claimed.*** Van Zee teaches that one can decrease inflammation using soluble TNFR to TNF. Applicant claims a method of ***increasing inflammation and the immune response against tumors by removing sTNFR.***

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Maraskovsky

Maraskovsky does teach that one can use an antibody column to remove materials from the blood. There is no teaching that it can be used to remove cytokine inhibitors to kill tumor cells.

For the same reasons that the examiner allowed the claims in the Howell patent over the combination of Lentz and Selinsky, so are the claims in this application allowable over Selinksky, Van Zee, Lentz, and Maraskovsky.

Feinman

Feinman does not make up for the deficiencies of the references discussed above. Feinman is not drawn to an *in vivo* situation, nor to treatment of tumor cells. Numerous studies have failed to demonstrate that interferon is useful in treating cancer.

Goodman

The examiner's characterization of the claimed method is inaccurate. The claims do **not** recite treating whole blood, but encompass treating whole blood or plasma. As described in the application, the blood is collected then separated into red cells and plasma, the plasma passed over the immunoaffinity column, then the red cells recombined with the plasma and the blood returned to the patient.

Goodman discloses making humanized antibodies. This does not make up for the deficiencies of the other references, however. Moreover, there is no motivation to use humanized antibodies, since these are immobilized, not administered to a patient.

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Proposed Amendment

Claims 17-22 have been added, which essentially correspond to U.S. Patent No. 6,379,708 to Howell, et al. This application claims priority to U.S.S.N. 09/083,307 filed May 22, 1998, before the earliest filing date of the Howell patent.

A proposed count is:

A method of enhancing an immune response in a patient comprising:

a. obtaining whole blood from the patient;

b. separating out the plasma;

c. contacting the plasma with antibody specifically binding to a targeted immune system inhibitor;

d. removing the inhibitor bound to the antibody from the plasma; and

e. returning the antibody-contacted plasma to the patient.

The basis for the claims is indicated in the claims as shown below in bold. The basis as found in Applicant's May 22, 1998, application is also shown below in italics.

17. A method of enhancing an immune response in a patient **(page 1, lines 6-7)** comprising:

a. obtaining whole blood from the patient **(page 18, lines 4-8)**; *(page 6)*

b. separating out the plasma. **(page 18, lines 7-8)**; *(page 6)*

c. contacting the plasma with antibody specifically binding to a targeted immune system inhibitor **(page 18, lines 8-11; page 6, lines 1-7)**; *(page 11, lines 23-26)*

d. removing the inhibitor bound to the antibody from the plasma **(pag 18, line 8-11)**; *(page 11, lines 23-26)* and

e. returning the antibody-contacted plasma to the patient. **(page 18, lines 11-15)**. *(page 7)*

18. The method of claim 17, wherein the antibody is immobilized in a solid support or membrane. **(page 9, lines 1-5)** *(page 11, lines 27-28)*

19. The method of claim 17, wherein the antibody is recombinant or a binding fragment. **(page 6, lines 18-20)**. *(page 11, lines 24-26)*

20. The method of claim 17, wherein the antibody is a mixture of antibodies immunoreactive with the targeted immune system inhibitor. **(page 6, line 27)** *(page 11, lines 22-29)*

21. The method of claim 17, wherein the patient is human. **(page 6, line 26)**. *(examples)*

22. The method of claim 17 wherein the targeted immune system inhibitor is selected from the group consisting of soluble receptors for tumor necrosis factors alpha and beta. *(page 11, lines 22-29)*

Double Patenting Rejection

As described by Chisum, "[d]ouble patenting is concerned with attempts to claim the same or related subject matter twice. Thus, the standard for comparison for the second patent is what was claimed in the first patent, not what was disclosed in the specification of the first patent." *Chisum*, 3:9.03[1][a]. "[A]n obviousness-type double patenting analysis entails two-steps." Eli Lilly & Co. v. Barr Laboratories, Inc., 251 F.3d 955, 58 U.S.P.Q.2d 1865 (Fed. Cir. 2001). First, one compares the later claim on the earlier claim to determine the differences. Second, one determines whether the differences in subject matter between the two claims demonstrates that the claims are patentably distinct. Id., *see* M.P.E.P. § 804, III (The rejection "must rely on a comparison **with the claims** in an issued or to be issued patent,...") (emphasis added). The Examiner failed to properly apply this standard of analysis.

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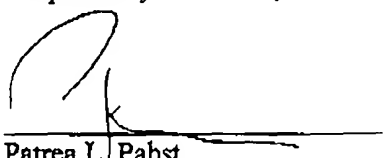
The claims in U.S. Patent No. 6,231,536 were interpreted by the examiner as requiring removal of the soluble tissue necrosis factor receptor using a molecular weight exclusion. There is nothing in such an interpretation that would make obvious the method as currently claimed. To the extent this rejection is maintained, it is respectfully requested that a final determination not be made until the outcome of the above-requested interference becomes available.

Allowance of claims 1-3, 5, 6, 8-11 and 17-22 and declaration of an interference with U.S. patent No. 6,379,708 is respectfully requested.

Respectfully submitted,



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CERTIFICATE OF FACSIMILE TRANSMITTAL

I hereby certify that this correspondence and any document referred to as being included therein is being facsimile transmitted to the Patent and Trademark Office on October 29, 2003.

Patrea Pabst

LEN102
077829/00006

METHOD AND SYSTEM TO REMOVE CYTOKINE INHIBITOR IN PATIENTS

Background of the Invention

The present invention is generally in the field of enhancing an immune response, and particularly relates to the removal of TNF inhibitors in a patient, such as a cancer patient, to promote inflammation and thereby induce remission of the cancer.

This application claims priority to U.S.S.N. 60/164,695, filed November 10, 1999.

Conventional cancer therapy is based on the use of drugs and/or radiation which kills replicating cells, hopefully faster than the agents kill the patient's normal cells. Surgery is used to reduce tumor bulk, but has little impact once the cancer has metastasized. Radiation is effective only in a localized area.

The treatments can in themselves kill the patient, in the absence of maintenance therapy. For example, for some types of cancer, bone marrow transplants have been used to maintain the patient following treatment with otherwise fatal amounts of chemotherapy. Efficacy has not been proven for treatment of solid tumors, however. "Cocktails" of different chemotherapeutic agents and combinations of very high doses of chemotherapy with restorative agents, for example, granulocyte macrophage colony stimulating factor ("GM-CSF"), erythropoietin, thrombopoetin, granulocyte stimulating factor, ("G-CSF"), macrophage colony stimulating factor ("M-CSF") and stem cell factor ("SCF") to restore platelet and white cell levels, have been used to treat aggressive cancers. Even with the supportive or restrictive therapy, side effects are severe.

such as a virus like HIV or parasite. The neutralizing agent is typically an antibody reactive with the receptor. the antibodies will typically be reactive with both the soluble and immobilized forms of the receptor. These include soluble tumor necrosis factor receptor ("sRTNF-R"), soluble interleukin-2 receptor ("sIL-2R"), soluble interleukin-1 receptor ("sIL-1R"), soluble interleukin-6 receptor ("sIL-6R"), or soluble interferon-gamma receptor ("sIFN-gammaR"). The advantage of selective removal or neutralization is that the same beneficial effect is obtained in treatment of the disorder but the treatment is much less expensive and safer since exogenous plasma or albumin does not have to be administered to the patient when there is selective removal, as in the case of ultrapheresis and the cytotoxic effects of radiation and chemotherapy are avoided.

The receptors can be removed by binding to the cytokine, an epitope thereof, or an antibody to the receptor. The antibodies to the receptors can be immobilized in a filter, in a column, or using other standard techniques for binding reactions to remove proteins from the blood or plasma of a patient, or administered directly to the patient in a suitable pharmaceutically acceptable carrier such as saline. As used herein, antibody refers to antibody, or antibody fragments (single chain, recombinant, or humanized), immunoreactive against the receptor molecules. In the most preferred embodiment, the antibody is reactive with the carboxy-terminus of the shed receptor molecules, thereby avoid concerns with signal transduction by the receptor is still present on the cell surface.

Antibodies can be obtained from various commercial sources such as Genzyme Pharmaceuticals. These are preferably humanized for direct administration to a human, but may be of animal origin if immobilized in an extracorporeal device. Antibodies may be monoclonal or polyclonal. The

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re the Application of:	)	Group Art Unit: 1642
HOWELL et al.	)	Examiner: Helms, L.
Serial No.: 09/444,144	)	
Filed: November 20, 1999	)	DECLARATION OF MARK D. HOWELL AND CHERYL L. SELINSKY (37 CFR § 1.132)
Attorney File No.: 4369-1 (formerly Cyto001)	)	
For: METHOD FOR ENHANCING IMMUNE RESPONSES IN MAMMALS	)	

CERTIFICATE OF FACSIMILE TRANSMISSION
I hereby certify that this paper is being facsimile transmitted to the Patent and Trademark Office on February 20, 2001.
SHERIDAN ROSS P.C.
KATHLEEN BUSSELL

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

We, Mark D. Howell and Cheryl L. Selinsky, each declare as follows:

1. I am a co-inventor of the above-referenced patent application and am familiar with the application.

2. This Declaration is being submitted in conjunction with an Amendment and Response After Final Rejection to an Office Action having a mailing date of December 20, 2000.

3. The following discussion is provided in traverse of the Examiner's rejection of Claims 1-3, 5, 10-27, 34, 37-38, 40-42, and 50-56 under 35 U.S.C. § 103. These comments have been discussed with the Examiner in the telephone interview of February 6, 2001, and this Declaration is provided at the Examiner's suggestion.

Discussion of Lentz

The Examiner contends that Lentz teaches the separation of blood into a plasma component and a cellular component. While Lentz acknowledges that it is possible to separate plasma from the blood, it is submitted that Lentz also *discourages* such a separation of blood (see col. 1, lines 51-62) on the basis that such a separation "has a serious impact on the platelet level in the blood," "could not be considered for widespread use," and is "not very attractive for clinical use." Therefore, the Lentz reference, at best, is highly ambiguous on this point.

Second, a separation of cellular and acellular components offers no benefit if used in the method of Lentz. Lentz teaches a method of treating whole blood by passing the blood through a filter that separates factors in the blood based on size. Therefore, there is no advantage to be obtained by first separating the blood into cellular and acellular components, and then passing the components over the filter. Indeed, such a separation would be an added and unnecessary step in the method of Lentz. As such, the use of Lentz by the Examiner as a teaching of an element of plasma separation in the stated rejection under 35 U.S.C. § 103 is not appropriate because the teachings of Lentz are, at most, ambiguous, and further, because no advantage in the Lentz process is obtained by separating cellular and acellular components of whole blood. Therefore, Lentz does not provide any *motivation* to combine the ambiguous discussion in Lentz with the other cited references in the manner suggested by the Examiner.

In contrast to Lentz, and in further support of the non-obviousness of the method claimed in the present application, there are *significant* advantages not recognized or suggested by the prior art to separating the acellular fraction from the cellular fraction prior to treatment of the bodily fluid. First, it is noted that the present method has the advantage over Lentz of selectively removing the targeted immune system inhibitor without affecting the action of desirable immune system stimulators and other blood components. This advantage is significantly enhanced by treating only the acellular portion of the blood. Specifically, certain of the molecules targeted for removal by the method of the present invention are soluble components which typically bind to an immune system stimulator. These soluble components often are homologues of *another* binding partner for the immune system stimulator, such that the interaction between the immune system stimulator and the other binding partner is inhibited by the binding of the soluble component to the immune system stimulator. Since the other binding partner is frequently a cell-associated binding partner (*i.e.*, is present on cell surfaces), it is desirable, and indeed, may be highly advantageous, to bind the soluble immune system inhibitor *without binding the homologous cell-associated binding partner*. For example, sTNFRI is a soluble receptor for TNFα and TNFβ, which is produced through a proteolytic cleavage of the membrane receptor (mTNFRI) for TNFα and β. This proteolysis releases the extracellular domain of the mTNFRI from the cell surface and allows it to diffuse freely into the extracellular space. The sTNFRI, thus produced, retains fully the ability to bind TNF α and β with high affinity. Binding of TNFα and β by the sTNFRI prevents TNFα and β from binding to the

mTNFRI. Consequently, the pro-inflammatory and apoptotic effects normally induced through the crosslinking of mTNFRI by TNFα and β also are inhibited. Due to the significant structural similarity between sTNFRI and mTNFRI, contact of whole blood with a binding partner reactive with sTNFRI would permit binding to both the sTNFRI in circulation *and* the mTNFRI present on cell surfaces. This would have dire consequences for the patient, and would contradict the goals of the present method for several reasons. First, binding of the binding partner to mTNFRI would block its engagement by TNFα and β, thus, effectively reducing TNF-induced immune responses. Second, binding of an immobilized binding partner to mTNFRI would effect the depletion of mTNFRI-bearing leukocytes from whole blood, thereby diminishing immune competence. Third, and most undesirable, binding of an immobilized binding partner to mTNFRI would crosslink the receptor and act, therefore, as an agonist of TNFα and β. This would produce very significant and potentially fatal toxicities similar to those observed in human clinical trials of infusional TNFα.

By separating the whole blood into acellular and cellular components in the claimed method, these issues are avoided and the advantages of selectively removing the targeted immune system inhibitor while *maintaining* the action of desirable immune stimulators and other blood components is achieved. Since Lentz does not teach or suggest any selective removal of any specific factor, these advantages can not be realized by the method of Lentz.

Discussion of Selinsky

The Examiner contends that the reference of Selinsky et al. teach that the soluble TNFRI is removed by Ultrapheresis [sic], and that with the knowledge of Lentz, one would know that soluble immune system inhibitors can be removed from whole blood. The Examiner has also pointed to the statement in Selinsky et al.: "[w]e, therefore, propose the development of methods and/or reagents capable of specifically removing sTNFRI, or antagonizing its effects *in situ*, as unconventional, yet promising, strategies for cancer immunotherapy."

It is submitted that, although the statement in Selinsky et al. may cause one of skill in the art to consider how to antagonize or remove sTNFRI *in situ*, such a statement is merely an invitation to experimentation and opens the door for one of skill in the art to consider a wide range of possible approaches. Indeed, Selinsky et al. provide absolutely no guidance as to how one of skill in the art would go about such a task, but rather generally state that the "therapeutic utility of manipulating

sTNFRI levels *in vivo* has been demonstrated" and that "sTNFRI effectively inhibits immune responses *in vivo* and...its modulation is a legitimate therapeutic avenue." It is submitted that one of skill in the art, when presented with an invitation to manipulate the effects of a soluble protein, would look to a variety of conventional approaches to remove or manipulate the effects of that soluble protein *in vivo*, because such approaches are the most clinically desirable means of treating a patient. Conventional therapeutic manipulation of the immune system typically involves the administration of an antibody, peptide, protein, or small molecule that is designed to have a particular action in the patient. In fact, significant research has been directed to systems that enable the delivery of such reagents, including liposomes, targeting antibodies, combinations of liposomes and antibodies, small particles, emulsions, and other vehicles.

One conventional approach to modulating an immune response *in vivo* is to introduce into the subject a reagent that achieves the goal of selectively antagonizing or removing a target molecule once it is administered to a subject. For example, one method for removing or blocking the action of a soluble protein *in vivo* is to administer an antibody that binds to and effectively neutralizes the action of the target protein. Alternatively, a peptide or other soluble binding partner that competes with the target protein for binding to the natural ligand can be administered. As yet another alternative, a small molecule could be designed that targets and neutralizes the action of the target protein. Drug design for such *in vivo* applications is a common therapeutic approach when a target such as a soluble protein is available.

In contrast, to turn to an *ex vivo* approach such as that claimed in the present application is not conventional, and indeed, would be much less likely to be considered because it would conventionally be considered to be less direct, more expensive, and more invasive than the *in vivo* approaches discussed above. Such a method requires far greater manipulation of the patient and of the critical bodily fluids of the patient than an *in vivo* approach. Therefore, to arrive at the claimed *ex vivo* method would not have been an obvious extension of the statements made in Selinsky et al. that are referenced above.

4. I hereby declare that all statements made herein of my own are true and that all statements made on information and belief are believed to be true; and further that the statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code, and that

such willful false statements may jeopardize the validity of the subject application or any patent issuing therefrom.

2/20/01
Date

Mark D. Howell

2/20/01
Date

Cheryl L. Selinsky